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(54) Title: EP₂-RECEPTOR AGONISTS AS NEUROPROTECTIVE AGENTS FOR THE EYE**(57) Abstract**

The invention relates to the use of EP₂ receptor agonists as neuroprotective agents. In particular said compounds are represented by the formulae (I), (III), (IV) and (V) wherein the broken line attachment to the cyclopentane ring or the omega chain indicates the α configuration and the solid line attachment to the cyclopentane ring or the omega chain indicates the β configuration, R is hydrogen or a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $-(CH_2)_mR_1$ wherein m is 0-10, and R₁ is an aliphatic ring having from about 3 to about 7 carbon atoms, or an aryl or heteroaryl ring having from about 4 to about 10 carbon atoms and wherein the heteroatom is selected from the group consisting of N, O and S.

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**EP₂-RECEPTOR AGONISTS AS
NEUROPROTECTIVE AGENTS FOR THE EYE**

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Field of the Invention

The present invention relates to the use of EP₂ receptor agonists to provide a neuroprotective effect to the eye of a mammal.

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Background of the Invention

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Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

20

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

25

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

35

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β -adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

It has long been known that one of the sequelae of glaucoma is damage to the optic nerve head. This damage, referred to as "cupping", results in depressions in areas of the nerve fiber of the optic disk. Loss of sight from this cupping is progressive and can lead to blindness if the condition is not treated effectively.

Unfortunately lowering intraocular pressure by administration of drugs or by surgery to facilitate outflow of the aqueous humor is not always effective in obviating damage to the nerves in glaucomatous conditions. This apparent contradiction is addressed by Cioffi and Van Buskirk [Surv. of Ophthalmol., 38, Suppl. p. S107-16, discussion S116-17, May 1994] in the article, "Microvasculature of the Anterior Optic Nerve". The abstract states:

The traditional definition of glaucoma as a disorder of increased intraocular pressure (IOP) oversimplifies the clinical situation. Some glaucoma patients never have higher than normal IOP and others continue to develop optic nerve damage despite maximal lowering of IOP. Another possible factor in the etiology of glaucoma may be regulation of the regional microvasculature of the anterior optic nerve. One reason to believe that microvascular factors are important is that many microvascular diseases are associated with glaucomatous optic neuropathy.

Subsequent to Cioffi, et al., Matusi published a paper on the
“Ophthalmologic aspects of Systemic Vasculitis” [Nippon Rinsho, 52 (8), p.
2158-63, August 1994] and added further support to the assertion that many
microvascular diseases are associated with glaucomatous optic neuropathy. The
summary states:

Ocular findings of systemic vasculitis, such as polyarteritis nodosa,
giant cell angitis and aortitis syndrome were reviewed. Systemic
lupus erythematosus is not categorized as systemic vasculitis,
however its ocular findings are microangiopathic. Therefore, review
of its ocular findings was included in this paper. The most common
fundus finding in these diseases is ischemic optic neuropathy or
retinal vascular occlusions. Therefore several points in diagnosis or
pathogenesis of optic neuropathy and retinal and choroidal vaso-
occlusion were discussed. Choroidal ischemia has come to be able to
be diagnosed clinically, since fluorescein angiography was applied in
these lesions. When choroidal arteries are occluded, overlying retinal
pigment epithelium is damaged. This causes disruption of barrier
function of the epithelium and allows fluid from choroidal
vasculatures to pass into subsensory retinal spaces. This is a
pathogenesis of serous detachment of the retina. The retinal arterial
occlusion formed non-perfused retina. Such hypoxic retina released
angiogenesis factors which stimulate retinal and iris
neovascularizations and iris neovascularizations may cause
neovascular glaucoma.

B. Schwartz, in “Circulatory Defects of the Optic Disk and Retina in
Ocular Hypertension and High Pressure Open-Angle Glaucoma” [Surv.
Ophthalmol., 38, Suppl. pp. S23-24, May 1994] discusses the measurement of
progressive defects in the optic nerve and retina associated with the progression
of glaucoma. He states:

Fluorescein defects are significantly correlated with visual field loss
and retinal nerve fiber layer loss. The second circulatory defect is a
decrease of flow of fluorescein in the retinal vessels, especially the
retinal veins, so that the greater the age, diastolic blood pressure,
ocular pressure and visual field loss, the less the flow. Both the optic

disk and retinal circulation defects occur in untreated ocular hypertensive eyes. These observations indicate that circulatory defects in the optic disk and retina occur in ocular hypertension and open-angle glaucoma and increase with the progression of the disease.

Thus, it is evident that there is an unmet need for agents that have neuroprotective effects in the eye that can stop or retard the progressive damage that occurs to the nerves as a result of glaucoma or other ocular afflictions.

Prostaglandins were earlier regarded as potent ocular hypertensives; however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma. (See, for example, Starr, M.S. Exp. Eye Res. 1971, 11, pp. 170-177; Bito, L. Z. Biological Protection with Prostaglandins Cohen, M. M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L. Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477-505). Such prostaglandins include PGF_{2α}, PGF_{1α}, PGE₂, and certain lipid-soluble esters, such as C₁ to C₅ alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the United States Patent No. 4,599,353 certain prostaglandins, in particular PGE₂ and PGF_{2α} and the C₁ to C₅ alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., Invest. Ophthalmol. Vis. Sci. 28(suppl), 284 (1987)].

The isopropyl ester of PGF_{2α} has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for

example, Bito, L. Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et al., Prodrug 5, 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular $\text{PGF}_{2\alpha}$ and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects.

Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

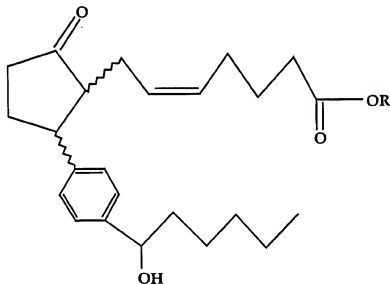
In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied by no or substantially reduced side-effects are disclosed. The co-pending USSN 386,835 (filed 27 July 1989), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $\text{PGF}_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application USSN 357,394 (filed 25 May 1989). Similarly, 11,15- 9,15- and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl $\text{PGF}_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications USSN No. 385,645 filed 27 July 1990, now U.S. Patent No. 4,494,274; 584,370 which is a continuation of USSN No. 386,312, and 585,284, now U.S. Patent No. 5,034,413 which is a continuation of USSN 386,834, where the parent applications were filed on 27 July 1989. The disclosures of these patent applications are hereby expressly incorporated by reference.

Finally, certain EP_2 -receptor agonists are disclosed in Nials et al, Cardiovascular Drug Reviews, Vol. 11, No. 2, pp. 165-179, Coleman et al, Comprehensive Medicinal Chemistry, Vol. 3, pp. 643-714, 1990 and Woodward et al, Prostaglandins, pp. 371-383, 1993.

Summary of the Invention

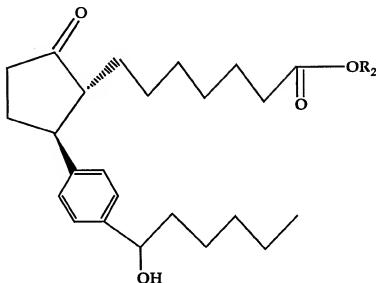
We have found that EP₂-receptor agonists are potent neuroprotective agents. We have further found that (+) trans-2-[4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoic acid, and certain other EP₂-receptor agonists, described below, and ester and unsaturated derivatives thereof, are especially useful in providing a neuroprotective effect to the eye of a mammal, e.g. a human.

The present invention relates to methods of providing a neuroprotective effect to the eye of a mammal, e.g. a human, which comprises administering an effective amount of a compound represented by the formula I



wherein, the wavy bands indicate the α or β configuration, R is hydrogen or a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $-(CH_2)_mR_1$ wherein m is 0-10, and R₁ is an aliphatic ring having from about 3 to about 7 carbon atoms, or an aryl or heteroaryl ring having from about 4 to about 10 carbon atoms, e.g. R₁ may be cyclohexyl, phenyl, thienyl, pyridyl or furanyl, or a pharmaceutically acceptable salt thereof and the dashed bond represents either a single or double bond which may be in the cis or trans position. Preferably R₁ is lower alkyl.

More preferably the method of the present invention comprises administering a compound represented by the formula II



5 wherein R_2 is hydrogen or a lower alkyl radical and the other symbols are as defined above.

Brief Description of the Drawing Figure

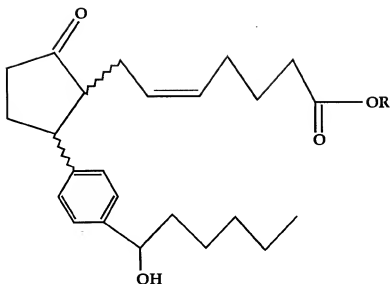
10 The Figure shows a comparison of the neuroprotective effect of EP_2 agonists with prostaglandins having no EP_2 agonist activity in preventing neuronal damage.

Detailed Description of the Invention

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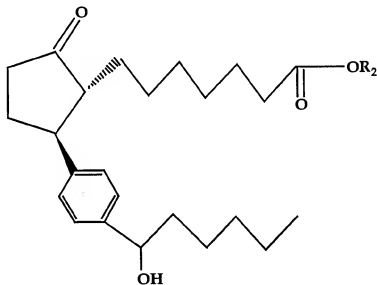
The present invention relates to the use of (\pm) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoic-acid, and ester and unsaturated derivatives thereof as neuroprotective agents. These therapeutic agents are represented by compounds having the formula I

20



as defined above. The preferred compounds used in accordance with the present invention are encompassed by the following structural formula II

5



wherein R_2 is hydrogen or a lower alkyl radical.

10

In all of the above formulae, as well as in those provided hereinafter, the straight lines represent bonds. Where there is no symbol for the atoms between the bonds, the appropriate carbon-containing radical is to be inferred. For example in formula I, the radical between the cyclopentyl ring and the



radical is a polymethylene (CH_2) radical, i.e. a hexylenyl radical. The dotted
 5 lines on the bond between carbons 5 and 6 (C-5), indicate a single or a double
 bond which can be in the cis or trans configuration. The radical adjacent to the
 double bond is a CH radical. If two solid lines are used that indicates a specific
 configuration for that double bond. Hatched lines at positions C-9 and C-11
 10 indicate the α configuration. If one were to draw the β configuration, a solid
 triangular line would be used.

In the compounds used in accordance with the present invention,
 compounds having the C-9 or C-11 substituents in the α or β configuration are
 contemplated. In all formulas provided herein, broken line attachments to the
 15 cyclopentane ring or the omega chain indicate substituents in the α configuration.
 Thickened solid line attachments to the cyclopentane ring or the omega chain
 indicate substituents in the β configuration.

For the purpose of this invention, unless further limited, the term "alkyl"
 20 refers to alkyl groups having from one to ten carbon atoms and includes "lower
 alkyl" radicals having from one to five carbon atoms, the term "cycloalkyl"
 refers to cycloalkyl groups having from three to seven carbon atoms, the term
 "aryl" refers to aryl groups having from four to ten carbon atoms. The term
 "saturated or unsaturated acyclic hydrocarbon group" is used to refer to straight
 25 or branched chain, saturated or unsaturated hydrocarbon groups having from one
 to about six, preferably one to about four carbon atoms. Such groups include
 alkyl, alkenyl and alkynyl groups of appropriate lengths, and preferably are alkyl,
 e.g. methyl, ethyl, propyl, butyl, pentyl, or hexyl, or an isomeric form thereof.

30 The definition of R may include a cyclic component, $-(\text{CH}_2)_m\text{R}_1$, wherein
 m is 0-10, R_2 is an aliphatic ring from about 3 to about 7 carbon atoms, or an
 aromatic or heteroaromatic ring. The "aliphatic ring" may be saturated or
 unsaturated, and preferably is a saturated ring having 3-7 carbon atoms,
 inclusive. As an aromatic ring, R_1 preferably is phenyl, and the heteroaromatic

rings have oxygen, nitrogen or sulfur as a heteroatom, i.e., R₁ may be thienyl, furanyl, pyridyl, etc. Preferably m is 0-4.

5 Preferred representatives of the compounds within the scope of the present invention are (±) trans-2-[-4(1-hydroxyhexyl)phenyl]-5-oxocyclopentaneheptanoic acid, unsaturated derivatives thereof, and lower alkyl esters of these compounds.

10 A compound which may be used in the pharmaceutical compositions and the methods of treatment of the present invention is (±) trans-2-[-4(1-hydroxyhexyl)phenyl]-5-oxocyclopentaneheptanoic acid.

15 A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Such salts are those formed with pharmaceutically acceptable cations, e.g., alkali metals, alkali earth metals, etc.

20 Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and
25 about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

30 For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

35 Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to,

benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place of or in conjunction with it.

The ingredients are usually used in the following amounts:

<u>Ingredient</u>	<u>Amount (% w/v)</u>
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	0-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-8.0
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations for use in the method of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 μ l.

The invention is further illustrated by the following non-limiting Examples.

Example 1**(±) TRANS-2-[-4(1-HYDROXYHEXYL) PHENYL]-5-OXOCYCLO-
PENTANEHEPTANOICACID AND LOWER ALKYL ESTERS
THEREOF**

5 The above acid compound is well known and may be purchased or synthesized by methods known in the art. The lower alkyl esters of this compound may be made by the esterification procedures described in the various patent applications described in the Background of the Invention.

Example 2**Method of Measuring a Neuroprotective Effect**

15 The dissection and dissociation of the rat hippocampal neuron cell cultures was carried out. Briefly, whole cerebral neocortices were removed from fetal rats, gestation age 15-19 days and kept in calcium-, magnesium-free Hanks' balanced salt solution. The hippocampi were removed under a dissecting microscope and the meninges were stripped away. When all the hippocampi
20 were removed, the tissues were incubated in 0.05% trypsin solution for 30 minutes at 37°C. At the end of 340 minutes, the trypsin solution was replaced with plating medium (minimal essential medium supplemented with 2% Hyclone horse serum, 1% fetal calf serum, 25 mM glucose, 1% glutamine and 1% penicillin/streptomycin and N₂ supplement). Then the tissues were triturated
25 with a Pasteur pipette 10 times and then again with a pipette whose tip has been fire polished to about half the normal diameter. The dissociated neuronal cells then were plated on poly D-lysine coated, 15 mm 24 well plates (2x10⁵ cells/well) in plating medium.

30 The cell cultures were kept at 37°C in a humidified, 5% CO₂-containing atmosphere. After 1-2 days, the horse serum level in the plating media was increased to 8%. After 4-7 days, the non-neuronal cell division was halted by 24 hours exposure to 10⁻⁶M Cytosine arabinoside (ARA-C), and the cells were then placed into growing medium with 4% horse serum, 1% fetal calf serum, 25 mM
35 glucose, 1% glutamine and 1% penicillin/streptomycin and N₂ supplement. Subsequent medium replacement was carried out every other day until the

neuronal cells matured (15-20 days). Only matured cell cultures were selected for study.

Exposure of the excitatory amino acids was performed in minimal essential medium (MEM). Extreme care was taken to wash out the growing medium from cultures before the addition of the excitatory amino acid since the neurons are very sensitive to disturbance. Matured cell cultures were exposed to either glutamate, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA), or kainic acid.

Cytotoxicity or cell injury was scored by light microscopy examination with trypan blue. In most experiments, the overall neuronal cell injury was quantitated by the amount of lactate dehydrogenase (LDH) released by the damaged cells into the media 24 hours after drug exposure.

LDH was measured at room temperature using Promega non-radioactive cytotoxicity assay kit. The absorbance of the reaction mixture was measured at 490 nm.

The Figure shows examples of LDH release after exposure of different excitotoxins and their antagonists.

As shown in the Figure, the effects of the EP₂ agonist AH 13205 on NMDA-induced neurotoxicity is shown in the top right panel. It is noted that PGF_{2 α} and PGF_{2 α} 1-OH are inactive, thereby indicating that this is a specific EP₂ receptor mediated effect.

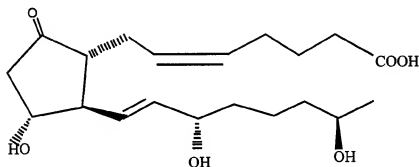
Example 3 **Determination of EP₂ Receptor Activity**

EP₂ receptor activity may be measured in accordance with the procedure disclosed in Woodward et al, Prostaglandins, pp. 371-383, 1993, which is hereby incorporated by reference in its entirety.

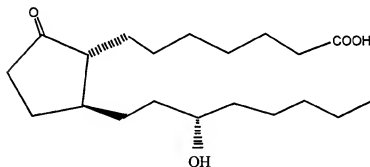
Example 4**Method of Measuring a Neuroprotective Effect**

5 The Experiment of Example 2 is repeated with other EP₂ Agonists, i.e. 19 (R)-OH PGE₂, AY 23626 and methyl 9-keto-11 α , 15 α -dihydroxy-16, 16 trimethyleneprosta-13-trans-enoate (butaprost) and the results are essentially as shown in the Figure for AH 13205.

10 19 (R) -OH PGE₂, AY 23626 and butaprost have the following structures, respectively.

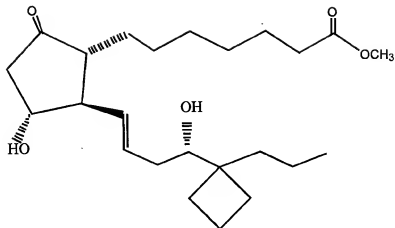


VI



VII

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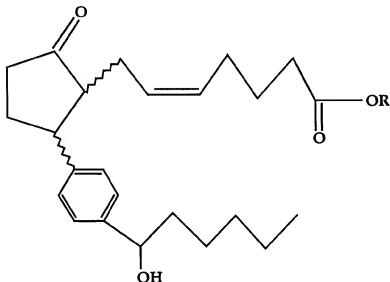
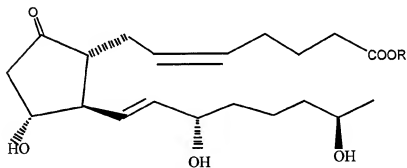
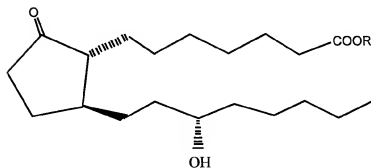
VIII

However, as with (+) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoic acid, the corresponding 1-ester or, in the case of butaprost other 1-ester derivatives as well as the 1-acid derivative are also useful in the method of the present invention.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent from one of ordinary skill in the art that different pharmaceutical compositions may be prepared and used with substantially the same results. That is, other EP₂-receptor agonists, will effectively lower intraocular pressure in animals and are within the broad scope of the present invention.

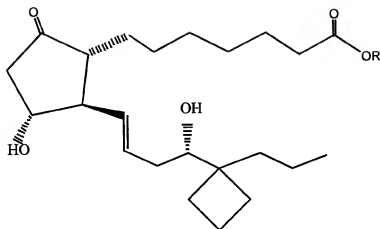
Claims:

1. A method of providing a neuroprotective effect to the eye of a mammal which comprises applying to the eye an amount sufficient to treat ocular hypertension of a compound of formula I, III, IV or V

**I****III****V**

18

IV

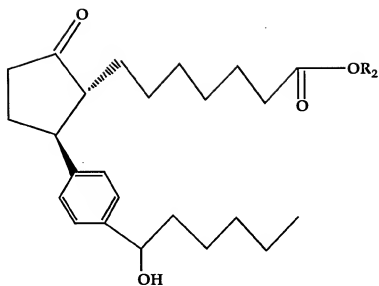


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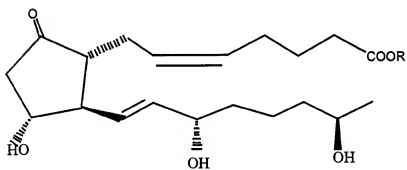
5 wherein the broken line attachment to the cyclopentane ring or the omega chain indicates the α configuration and the solid line attachment to the cyclopentane ring or the omega chain indicates the β configuration, R is hydrogen or a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $-(CH_2)_mR_1$ wherein m is 0-10, and R_1 is an aliphatic ring having from about 3 to about 7 carbon atoms, or an aryl or heteroaryl ring having from about 4 to about 10 carbon atoms and wherein the heteroatom is selected from the group consisting of N, O and S.

15 2. The method of Claim 1 wherein said compound is a prostaglandin derivative of the formula II, VI, VII or VIII

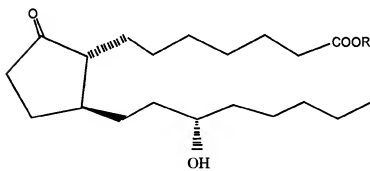
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II



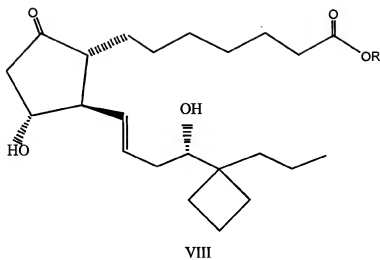
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VII

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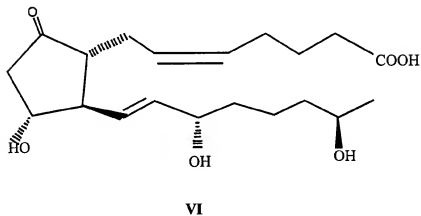
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wherein R₂ is a hydrogen or a lower alkyl radical.

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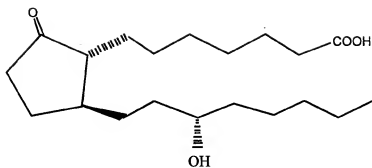
3. The method of Claim 2 wherein said compound is



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4. The method of Claim 2 wherein said compound is

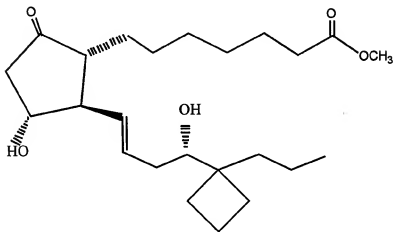
21



VII

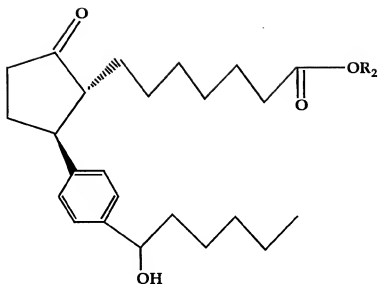
5. The method of claim 2 wherein said compound is

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VIII

6. The method of claim 2 wherein said compound is



II

wherein R₂ is hydrogen or a lower alkyl radical.

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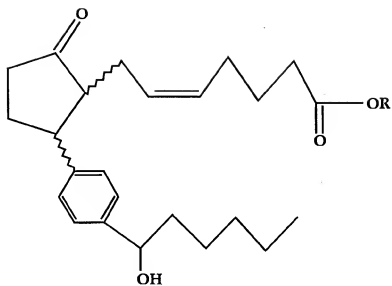
7. A method for providing a neuroprotective effect to the eye of a mammal which comprises applying to the eye an amount sufficient to treat ocular hypertension of a compound having EP₂ receptor agonist activity.

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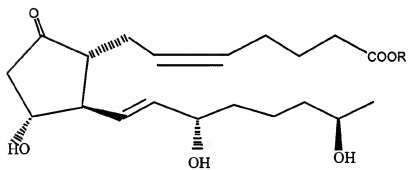
8. A method of protecting the retinal or optic nerve cells in a mammal suffering a noxious action or at risk of experiencing a noxious action on said nerve cells comprising administering to said mammal an effective amount of a compound of formula I, III, IV or V to inhibit or prevent nerve cell injury or death

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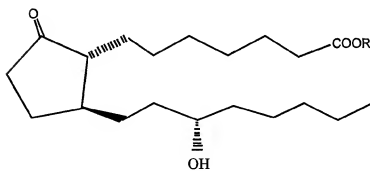
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I

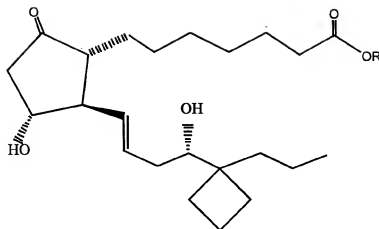


III



IV

5



V

wherein the broken line attachment to the cyclopentane ring or the omega chain indicates the α configuration and the solid line attachment to the cyclopentane ring or the omega chain indicates the β configuration, R is hydrogen or a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $-(CH_2)_mR_1$ wherein m is 0-10, and R_1 is an aliphatic ring having from about 3 to about 7 carbon atoms, or an aryl or heteroaryl ring having from about 4 to about 10 carbon atoms and wherein the heteroatom is selected from the group consisting of N, O and S.

9. The method of claim 8 wherein the noxious action is the elevated intraocular pressure of glaucoma.

10. The method of claim 8 wherein the noxious action is ischemia associated with glaucoma.

11. The method of claim 8 wherein the noxious action is diabetic retinopathy.

12. The method of claim 8 wherein the noxious action is non-glaucomatous ischemia.

13. The method of claim 8 wherein the noxious action is microangiopathic in nature and is a symptom of the disease chosen from the

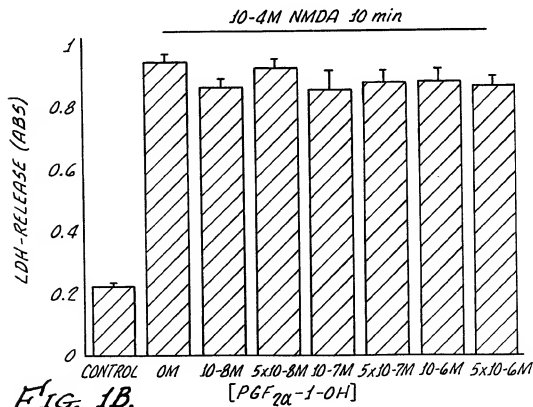
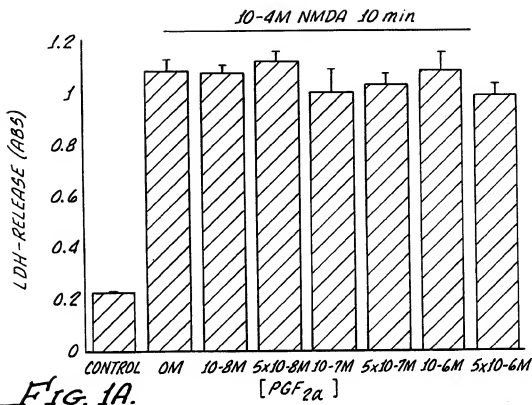
group consisting of polyarteritis nodosa, giant cell angitis, aortitis syndrome and systemic lupus erythematosus.

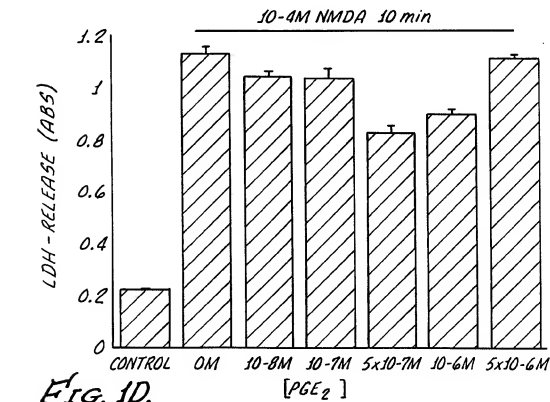
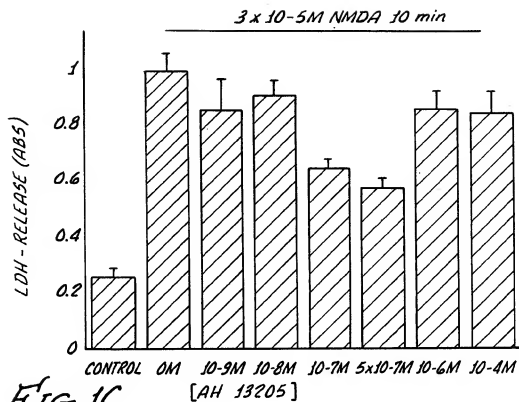
5 14. The method of claim 8 wherein oral administration is used to supply the compound to the mammal systemically.

 15. The method of claim 8 wherein intrabulbar injection in the eye is used to supply the compound to the mammal.

10 16. The method of claim 8 wherein parenteral administration is used to supply the compound to the mammal systemically.

 17. The method of claim 8 wherein intramuscular injection is used to supply the compound to the mammal systemically.





INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/24978

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	D.F.WOODWARD ET AL.: "The molecular biology and ocular distribution of prostanoïd receptors" SURVEY OF OPHTHALMOLOGY, vol. 41, no. supplement 2, February 1997, pages S15-S21, XP002101437 see abstract see page S19, right-hand column, paragraph 2 --- -/--	1-17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the international search

28 April 1999

Date of mailing of the international search report

18/05/1999

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Authorized officer

Tzschoppe, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/24978

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AKINORI AKAIKE ET AL.: "Prostaglandin E2 protects cultured cortical neurons against N-methyl-D-aspartate receptor-mediated glutamate cytotoxicity" BRAIN RESEARCH, vol. 663, no. 2, 1994, pages 237-243, XP002101438 see abstract see page 241, right-hand column - page 242, right-hand column ---	1-17
Y	D.F.WOODWARD ET AL.: "Molecular characterisation and ocular hypotensive properties of the prostanoid EP2 receptor" J. OCUL. PHARMACOL. THER., vol. 11, no. 3, 1995, pages 447-454, XP002101439 see abstract ---	1-17
Y	US 5 462 968 A (WOODWARD DAVID F) 31 October 1995 see column 8, line 7 - line 15; claims 1-3 ---	1-17
P, Y	US 5 698 598 A (WOODWARD DAVID F) 16 December 1997 see claims 1-15 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/24978

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5462968 A	31-10-1995	AU 685591 B AU 1725795 A CA 2181569 A EP 0789687 A JP 9509652 T WO 9519964 A	22-01-1998 08-08-1995 27-07-1995 20-08-1997 30-09-1997 27-07-1995
US 5698598 A	16-12-1997	NONE	